PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PPD70156/WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/003497	International filing date *(day/month/year)* 16.08.2004	Priority date *(day/month/year)* 30.09.2003
International Patent Classification (IPC) or national classification and IPC C07C51/367		
Applicant SYNGENTA LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.07.2005	12.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, M Telephone No. +49 89 2399-8335

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003497

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-5 as originally filed

   Claims, Numbers

   1-7 filed with telefax on 02.11.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003497

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 US 4 532 346
D2 US 4 625 053
D3 FR 763 374
D4 US 4 505 743
D5 XP 00 223 77 22

V.1 Novelty

D1 and **D2** describe the preparation of optically active 2-(4-hydroxyphenoxy)-propionic acid or salts thereof by reacting hydroquinone with an optically active 2-halopropanoic acid in presence of a base (**D1**, col.3, lines 63-68 and claim 1; **D2**, claim 1). **D3** relates to the improvement of the enantiomeric resolution on an industrial basis using sulfite as a reductive agent to avoid oxidative impurities (**D3**, page 4, lines 8-11). **D4** and **D5** disclose the further use of 2-(4-hydroxyphenoxy)-propionic acid in the preparation of herbicids, such as clodinafop.

Since none of the above-cited documents disclose the use of a "mild reducing agent", as defined in the present claim 1, in the production of optically pure (R) 2-(4-hydroxyphenoxy)-propionic, novelty could be recognized for the subject-matters of claims 1 to 7.

V.2 Inventive step

The closest related process is known from **D2**. In order to avoid side-reactions, such as disubstitution of hydroquinone, precipitation is performed during the reaction using a base (**D2**, col.2, line 50 and claim 1; col.4, lines 16-22). The present claimed process differs from the one of **D2** in that it requires a mild reducing agent and avoids precipitation. The technical problem presently posed is accordingly to provide a production process of optically pure (R) 2-(4-hydroxyphenoxy)-propionic on an industrial scale, i.e. simple purification procedure, reduced costs and high ee. The solution proposed is the use of a mild reducing agent. The claimed process has been shown to solve the technical problem posed by using sodium bisulfite as reducing agent. Former processes of production of (R)2-(4-hydroxyphenoxy)-propionic are suffering from the formation of coloured by-products due to the oxidation of

hydroquinone and disubstituted hydroquinone. None of these processes disclose the use of a mild reducing agent as a potential solution to solve these problems. Different mild reducing agents can be used (claim 5), sulphite or bisulphite being more preferred (claim 6). It is known from the skilled person from his general knowledge that sulfite is a protecting agent against oxidation. This is supported by **D3** (**D3**, page 4, lines 8-11). This document is directed to the resolution of optical isomers in general and of adrenaline in particular (**D3**, page 1; page 2, lines 34-43). **D3** is accordingly not directed to an asymmetric reaction and is not confronted to the removal of coloured-impurities. The reducing properties of sodium sulphite are not determining in the choice of the reagents used therein. The purpose of sodium bisulphite in **D3** is to adjust the pH (**D3**, page 4, lines 42-49 or claim 4; claim 1). The skilled person confronted with the present technical problem of formation of oxidative impurities would therefore not be inclined to combine the teachings of **D2** and **D3** and come up to the proposed solution. An inventive step is accordingly acknowledged.

Item VIII

1. The expression "such as" used in claim 1 has no limiting effect on the scope of this claim. The features following this expression are accordingly entirely optional. Since these features are relevant, they have been formulated as part of dependent claims 4 and 5. They should accordingly have been removed from claim 1 in order to fullfill the requirement of conciseness of Article 6 PCT.

2. For consistency and clarity reasons, a reference to the definition provided in claim 1 for the "mild reducing agent" used in claim 7 should have been introduced therein, i.e. "mild reducing agent as defined in claim 1" (Article 6 PCT).

CLAIMS

1. A process for producing R-2-(4-hydroxyphenoxy)propanoic acid or a salt thereof by reaction of hydroquinone or a salt thereof with a S-2-halopropanoic acid or a salt thereof in the presence of a mild reducing agent wherein the mild reducing agent is a neutral or a charged low oxidation state sulphur species, such as sulphur dioxide, a sulphite, a bisulphite, a hydrosulphite, a metabisulphite, a sulphenic acid, a sulphinic acid, for example formamidine sulphinic acid, or a low oxidation state phosphorous species such as a phosphite or hypophosphite, or hydrazine, a hydrazine derivative, or ascorbic acid.

2 A process according to claim 1 wherein the S-2-halopropanoic acid is S-2-chloropropanoic acid.

3 A process according to claim 1 or claim 2 wherein the excess hydroquinone is recovered for recycle.

4 A process according to any preceding claim wherein the mild reducing agent is a neutral or a charged low oxidation state sulphur species, a low oxidation state phosphorous species, hydrazine, a hydrazine derivative or ascorbic acid.

5 A process according to claim 4 wherein the mild reducing agent is sulphur dioxide, a sulphite, a bisulphite, a hydrosulphite, a metabisulphite, a sulphenic acid, a sulphinic acid, a phosphite, hypophosphite, hydrazine, a hydrazine derivative or ascorbic acid.

6 A process according to claim 5 wherein the mild reducing agent is an alkali metal sulphite or bisulphite.

7 A process for the manufacture of quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl by a) producing R-2-(4-hydroxyphenoxy)propanoic acid by reaction of hydroquinone or a salt thereof with S-2-halopropanoic acid or a salt thereof,

in the presence of a mild reducing agent, b) reacting the R-2-(4-hydroxyphenoxy)propanoic acid with the appropriate halo-aryl or halo-heteroaryl moiety to give a R-2-((4-aryloxy or heteroaryloxy)phenoxy)propanoic acid and c) esterification of the acid from step b) to give quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl.